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POLYMORPHISMS OF 5'-UTR OF *RAD51* GENE IN PROSTATE CANCER

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❀ **Background.** Notwithstanding that prostate cancer is largely studied all over the world for many decades, its etiology is not known and there is an intensive work to elucidate the cause and molecular markers for the development of this male cancer. Polymorphisms in DNA repairing genes may affect the DNA repairing capacity that in turn contributes to cancer development. This study aims to explore the polymorphisms of homologous recombination (HR) *RAD51* gene (rs1801320 and rs1801321) as a possible risk factor for developing prostate cancer. Sequencing of 5'-UTR of *RAD51* gene (rs1801320 and rs1801321) was studied in 80 DNA samples of prostate cancer and 50 DNA samples from a control group. Our results revealed a significant correlation between rs1801320 G>C polymorphism and the presence of prostate cancer in the Jordanian population ($p = 0.041$, $X^2 = 6.377$). On the other hand, the rs1801321 G>T polymorphism was not associated with the presence of prostate cancer in the study population ($p = 0.27$, $X^2 = 2.6$). In conclusion, our results shed a light on the possible role of *RAD51* gene polymorphisms in the development of prostate cancer; however, a larger representative study is needed to elucidate a possible role of *RAD51* gene polymorphisms in development and prognosis of prostate cancer.

❀ **Keywords:** *RAD51*; 5'-UTR polymorphism; prostate cancer; rs1801320; rs1801321.

INTRODUCTION

Prostate cancer (PC) in Jordan, as the developed countries, is the most commonly diagnosed cancer in men. The incidence of prostate cancer in Jordan has increased in the last decades, and it shows a rise in the number of prostate cancer cases among Jordanian males from 123 in 2000 to 218 in 2010 [1]. As a heterogeneous type of cancer, prostate cancer has no identified susceptibility genes or etiologic agents [2-4]. However, some genetic loci have been studied in prostatic carcinoma including *BRCA1, BRCA2, ELAC2, RNASEL* and *MSR1* genes [3]. Nevertheless, low penetrance of those genes was demonstrated in prostate cancer [5-7]. Therefore, many studies have investigated the possible association between the mutations or polymorphisms in DNA repair genes and the development of prostatic carcinoma [8].

Naturally, continuous exposure of cells to genotoxic factors can lead to DNA damage which, in turn, activates DNA repairing mechanisms. RAD51 is a homologous recombination (HR) protein that is encoded by *RAD51* gene located on chromosome 15 [9]. RAD51 is a key recombinase in the process of double-strand breaks (DSBs) repair by homologous recombination; other accessory proteins are involved in the DSBs such as RAD51 family proteins and breast cancer associated proteins BRCA1 and BRCA2 [10, 11]. Genetic alteration in *RAD51* has been shown to be related to cancer development by several studies [12–21]. For instance, RAD51 and RAD51-related proteins have been found to be overexpressed and deregulated in some types of cancers like colorectal, pancreatic and breast cancers [22-26]. Basically, mutations of *RAD51* can lead to defects in mitotic and meiotic recombination, DSB repair and hypersensitivity to ionization [11, 27-30]. Genetic predisposition of DNA repairing proteins in cancer has been suggested after many studies of single nucleotide polymorphisms (SNPs) in certain genes like (*RAD51, XRCC1, XRCC2* and *XRCC3*) [12, 16, 31-36]. A significant association has been found between breast cancer and polymorphic changes at G135C (rs1801320) and G172T (rs1801321) positions in the 5'-UTR region of the *RAD51* gene [12, 16, 37]. Similarly, rs1801320 and rs1801321 polymorphisms of the *5'-UTR-RAD51* area have been investigated in many other cancers including prostate cancer [19, 38, 39].

The aim of the current case-control study was to elucidate a possible association between prostate cancer and G135C (rs1801320) and G172T (rs1801321) polymorphisms at the 5'-UTR area of the *RAD51* gene in the Jordanian population.

MATERIALS AND METHODS

Tumor Samples and Patients

Formalin Fixed Paraffin Embedded (FFPE) tissue samples from 80 prostate cancer patients who underwent prostatectomy were provided by the Department of Pathology at King Abdullah University Hospital from January 2003 through December 2016. Most of them had advanced stages of the disease (Table 1). The tissue diagnoses were submitted based on a pathologic assessment verified by a pathologist at the Department of Pathology. The majority of the samples showed tumor component of over 60%. The mean age of the enrolled patients with prostate cancer was 72 years (range, 55-95 years). The control group included 50 blood samples from age-matched (mean age = 70) males with no known history of cancer.

All samples were collected after signing an informed consent which was approved by the Research and Ethics Committee at Yarmouk University and IRB approval from King Abdullah University Hospital at Jordan University of Science and Technology.

DNA Extraction

DNA was extracted from (FFPE) by using the QIAmp extraction DNA kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocols. Briefly, four to six sections of FFPE tissue were deparaffinized three times with 1mL of Xylene, followed by three times wash with absolute ethanol. The samples then were incubated overnight at 56 °C, with proteinase K lysis buffer, followed by incubation at 90 °C for 45 minutes. The lysate was transferred to the column, washed as requested in the protocol. Final elution of the DNA was performed by adding TE buffer and centrifugation at 12,000 g. All collected samples were stored at −80 °C until use.

PCR AND SEQUENCING

For the amplification of the target area, specific primers were requested as described before [16]: F-5'-AGCTGGGAACTGCAACTCAT-3', R-5'-CGCCTCACACACTCACCTC-3' (IDT, Illinois, USA) (Figure 1). PCR reaction was conducted in a total volume of 30L by using 2X-master-mix from (BioLabs, New England, USA) under the following conditions: Initial denaturation at 94 °C for 3 minutes, 40 cycles of denaturation, annealing and extension for 30 seconds at 94 °C, 60 °C and 68 °C, respectively. Followed by final extension was at 68°C for 5 minutes. The PCR products were analyzed and resolved by running the samples on 1.5% agarose gel.

Sanger DNA sequencing was analyzed as an external service by (GENEWIZ, NJ, USA). The output DNA sequencing service was analyzed by UGENE software.

Statistical Analysis

GraphPad Prism 6 software was used to calculate the p-value, Hardy–Weinberg Equilibrium HWE, the odd ratio (OR) and 95% confidence interval (CI) by performing Chi-square test and Fisher's exact test. P value considered significant when it is < 0.05.

Table 1

Clinicopathological data of the patients

Clinicopathological data (n = 72 ± 10.5)		
Age (years)	72	
PSA (ug/L)	61.6	
Gleason Score	*n*	%
3+3	10	13
3+4	20	25
4+3	3	4
4+4	10	13
4+5	21	26
5+4	3	4
5+5	12	15

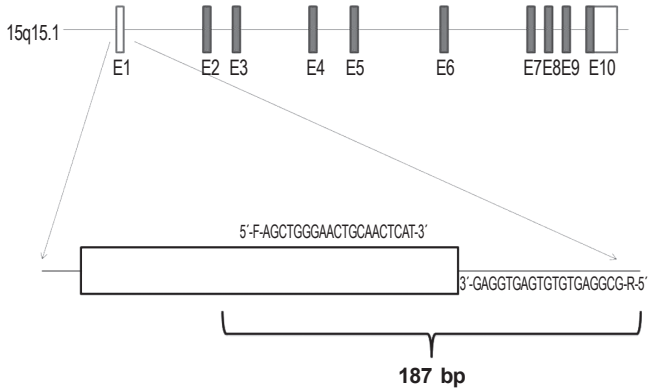

Fig. 1. Illustration of *RAD51* gene describing the location of the target area on chromosome 15 including 10 exons. The primers positions and the expected product size (187 bp) are shown. The amplified area is including part of exon 1 and intron 1

RESULTS

Genotypes frequencies of 135G>C (rs1801320)

PCR product was resolved by 1.5% agarose to confirm the amplification of the product of 187 bp (Figure 2).

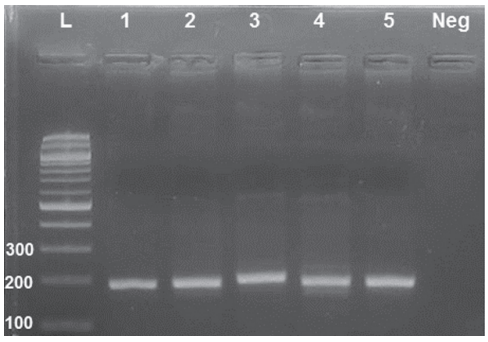

Fig. 2. A representative gel electrophoresis for the PCR product of the target sequence located in the 5'-UTR area of the *RAD51* gene. Lane L: 100 bp marker, Lanes 1-5 positive product and Lane Neg: Negative control

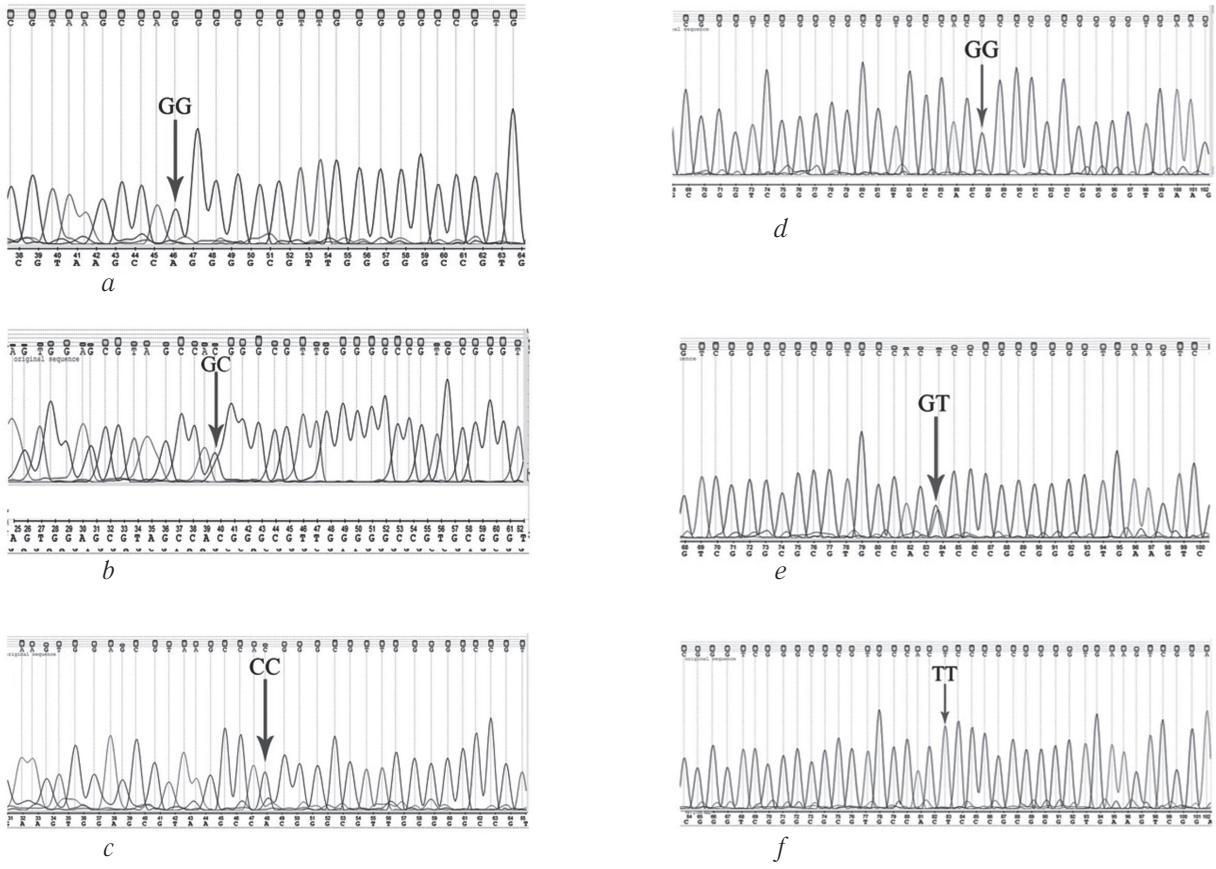

Fig. 3. Chromatogram of the target sequences in the 5'-UTR-RAD51 area. *a*, *b* and *c* represent the GG, GC and CC genotypes of the rs1801320 G>C polymorphism. *d*, *e* and *f* represent the GG, GT and TT genotypes of the rs1801321 G>T polymorphism

Table 2

Percentage distribution of rs1801320 (G135C) genotypes in prostate cancer (PC) cases and control group, showing a significant difference between prostate cancer cases and control group

	SNP	Tumors	%	Control	%	
rs1801320	G135G	74	92.5	44	88.0	$p = 0.041$, $X^2 = 6.377$
	G135C	1	1.3	5	10.0	
	C135C	5	6.2	1	2.0	
	Total	80	100	50	100	
Allele frequencies analysis: $p = 1.0$, OR = 0.98, 95% CI: (0.3671 to 2.620)						

In the study population, there was no significant difference in the mean age between patients and control group, 72 and 70 years, respectively. The clinicopathological data showed the distribution of Gleason score between 3+3 and 5+5 and PSA concentration (mean 61.6 μg/L) (Table 1). The sequences of the target SNPs in the 5'-UTR area of the *RAD51* gene were confirmed by Sanger sequencing and shown in (Figure 3). The genotypes frequencies of the rs1801320 G>C polymorphism in the patients group showed the following distribution: the homozygous G135G variant was 74 (92.5%), the heterozygous G135C variant was 1 (1.3%) and the homozygous C135C variant was 5 (6.2%) and shown in (Table 2). While the control group showed the following distribution of the G135C genotypes: the homozygous G135G was 44 (88%), the heterozygous G135C variant was 5 (10%) and the homozygous C135C variant was 1 (2%) and shown in (Table 2). Accordingly, our results showed a significant association between 135 G>C genotype and the presence of prostate cancer ($p = 0.041$ $X^2 = 6.377$). While the frequency of C allele did not show any significant association with the presence of prostate cancer ($p = 1.0$ and OR = 0.9895% CI: (0.3671 to 2.620)).

Genotypes frequencies of 172G>T (rs1801321)

In the patient group, the rs1801321 G>T genotypes frequencies for the homozygous G172G, heterozygous G172T and homozygous T172T variants were 17 (21.25%), 53 (66.25%) and 10 (12.5%), respective-

Table 3

Percentage distribution of rs1801321 (G172T) genotypes in prostate cancer (PC) cases and control group, showing no significant difference between prostate cancer cases and control group

	SNP	Tumors	%	Control	%	
rs1801321	G172G	17	21.25	15	30.0	$p = 0.27$, $X^2 = 2.6$
	G172T	53	66.25	26	52.0	
	T172T	10	12.5	9	18.0	
	Total	80	100	50	100	
Allele frequencies analysis: $p = 0.89$ OR = 1.07, 95% CI: (0.6459 to 1.766)						

ly (Table 3). While the control group showed the following distribution of the G135C genotypes: the homozygous G172G variant was 15 (30%), the heterozygous G135C variant was 26 (52%) and the homozygous C135C variant was 9 (18%) and shown in (Table 3). For the 172 G>T polymorphism, our results did not show any significant association between 172 G>T genotypes ($p = 0.27$, $X^2 = 2.6$) or allelic frequencies and the susceptibility of prostate cancer in the study population ($p = 0.89$ OR = 1.0795% CI: (0.6459 to 1.766)).

DISCUSSION

The current study aimed to evaluate the association between the polymorphisms of 5'-UTR of *RAD51* gene and the development of prostate cancer. Our results showed a significant association between G135C variant (rs1801320) and the development of prostate cancer in the Jordanian population. On the other hand, neither the G172T variant nor T allele frequency showed any significant association with the susceptibility of prostate carcinoma. These results are consistent with the previous findings by Nowacka et al [19].

A number of DNA repairing genes have been studied to find an association with the risk of prostate cancer. However, from the long list of investigated genes, few variants in those genes are associated with development or prognosis of prostate cancer [40, 41]. In many previous reports, an association was demonstrated between the 5'-UTR polymorphisms of *RAD51* gene and the susceptibility of breast cancer [12, 16]. Therefore, we aimed to evaluate a possible role of these variants in the development of prostate cancer. In addition, RAD51 overexpression has been demonstrated in high-grade prostate cancer [42]. Moreover, mRNA and protein levels of RAD51 and other homologous recombination-related proteins were elevated in malignant prostate cancer cell line [43].

The impact of G135C variant (rs1801320) on the development of cancer is not fully understood. However, a functional study has shown higher expression of the RAD51 protein by replacement of G with C at position 135 and G with T at position 172 of the 5'-UTR area of *RAD51* gene [44]. Those findings, hypothetically, proposed a crucial impact of RAD51 overexpression in the development of prostate cancer as well as many other cancers. Regardless of the molecular mechanism of the effect of the overexpression of RAD51, the DNA repair system is supposed to lessen the risks of mutations that are generated from environmental risk factors, which speculates a positive impact of RAD51 expression. This dilemma requires a full understanding of the mechanism of RAD51 during DNA repair. Partial resolution of BRCA2 and RAD51 repairing mechanism was described by Lord et al, they described two different sites (motifs) within BRCA2 that bind different forms of RAD51, which may require a balance between this interaction for proper function of the BRCA2-RAD51 complex in DNA repair [10]. This may explain the possible negative impact of RAD51 overexpression in some cancers. Pieces of evidence are accumulated about the role of RAD51 overexpression in different cancers, besides the association between the 5'-UTR polymorphisms and the susceptibility of cancer [12, 15, 16, 18-21, 31, 32, 36-38, 42]. More functional studies are required to understand the role of RAD51 during the pathogenesis of cancer. Our findings do not exclude the impact of environmental risk factors and other genetic alterations in the development of prostate cancer. However, we highlight the possible contribution of *5'-UTR-RAD51* variants in the development of prostate cancer.

In conclusion, our results underscore the possible association between G135C variant (rs1801320) and the susceptibility of prostate cancer in the Jordanian population. More large-scale studies are required to elucidate the role of G135C variant (rs1801320) and RAD51 expression in the development of prostate cancer.

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